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Peripheral oxytocin and vasopressin: Biomarkers of psychiatric disorders? A comprehensive systematic review and preliminary meta-analysis

Rutigliano Grazia[a,b,1], Rocchetti Matteo[a,c,1], Paloyelis Yannis[d], Gilleen James[a,f], Sardella Alberto[a], Cappucciati Marco[a,c], Palombini Erika[a,c], Dell'Osso Liliana[b], Caverzasi Edgardo[c], Politi Pierluigi[c], McGuire Philip[a], Fusar-Poli Paolo[a,e,*]

[a] Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, PO63, De Crespigny Park, SE58AF London, UK
[b] Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67-56126 Pisa, Italy
[c] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
[d] Neuroimaging Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, PO89, De Crespigny Park, SE58AF London, UK
[e] OASIS clinic, SLaM NHS Foundation Trust, 190 Kennington Lane, SE11 5DL London, UK
[f] Department of Psychology, University of Roehampton, UK

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ABSTRACT

A large array of studies have investigated peripheral oxytocin (OT) and vasopressin (ADH) as potential biomarkers of psychiatric disorders, with highly conflicting and heterogenous findings. We searched Web of KnowledgeSM and Scopus® for English original articles investigating OT and/or ADH levels in different biological fluids (plasma/serum, saliva, urine and cerebrospinal fluid) across several psychiatric disorders. Sixty-four studies were included. We conducted 19 preliminary meta-analyses addressing OT alterations in plasma/serum, saliva, urine and cerebrospinal fluid of 7 psychiatric disorders and ADH alterations in plasma/serum, saliva, urine and cerebrospinal fluid of 6 psychiatric disorders compared to controls. Hedge's g was used as effect size measure, together with heterogeneity analyses, test of publication biases and quality control. None of them (except serum OT in anorexia nervosa) revealed significant differences. There is no convincing evidence that peripheral ADH or OT might be reliable biomarkers in psychiatric disorders. However, the lack of significant results was associated with high methodological heterogeneity, low quality of the studies, small sample size, and scarce reliability of the methods used in previous studies, which need to be validated and standardized.

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* Correspondence to: Department of Psychosis Studies, Institute of Psychiatry, PO63, De Crespigny Park, SE58AF London, UK.
E-mail address: paolo.fusar-poli@kcl.ac.uk (P. Fusar-Poli).
[1] Joint first authors.

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1. Introduction

Oxytocin (hereafter OT) and vasopressin (hereafter ADH) are neuropeptides mainly synthesized in the brain's hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei (Ludwig and Leng, 2006). They are released in systemic circulation through the posterior pituitary gland, where they act as hormones regulating a range of physiological functions (Gimpl and Fahrenholz, 2001; Leng et al., 2015). They are also released in the central nervous system, acting on multiple brain regions as neuromodulators and influencing a range of neurophysiological processes and behaviours (Stoop, 2012), including feeding, anxiety, aggression, social recognition and the stress/fear response to social stimuli (Hashimoto et al., 2012).

Evidence from animal studies has demonstrated the significant role that OT and ADH play in the regulation of social behaviour and cognition (Chang and Platt, 2014). An increasing number of studies have also began to dissect the roles of OT and ADH in human social behaviour (Heinrichs et al., 2009). These neuropeptides are associated with complex social and emotional processing in healthy people which if impaired may account for some of the symptoms present in psychiatric disorders (Meyer-Lindenberg et al., 2011). Furthermore, there is also growing interest in the potential for synthetic neuropeptides in treatment of psychosis (for a comprehensive review see (Gumley et al., 2014)), autism spectrum disorders (ASD) (Thompson et al., 2006; Uzunova et al., 2015), and affective and anxiety disorders (Griebel et al., 2012).

In animals there are multiple methods that allow to reliably either assess or manipulate central OT and ADH levels and their effects on behaviour (e.g. intracerebral microdialysis (Veenema and Neumann, 2008), targeted delivery of neuropeptide agonists or antagonists (Song et al., 2014), gene knockout (Wersinger et al., 2002), and viral gene transfer (Pagani et al., 2014)). However, these are not available in humans, hence researchers have turned to peripheral assays as proxy measures. Specifically, plasma/serum (Rubin et al., 2014), saliva (Fujisawa et al., 2014), urine (Hoffman et al., 2012) or cerebrospinal fluid (CSF) (Sasayama et al., 2012) OT and ADH levels have been recently tested as putative biomarkers in ASD (Alabdali et al., 2014; Boso et al., 2007; Modahl et al., 1998), Psychosis (Elman et al., 2003; Goldman et al., 2008; Rubin et al., 2013; Walss-Bass et al., 2013), bipolar disorder (BD) (Rubin et al., 2014; Turan et al., 2013), major depressive disorder (MDD) (Goldstein et al., 2000; Ozsoy et al., 2009; Yuen et al., 2014), as well as in anxiety (Hoge et al., 2012, 2008), personality (Bertsch et al., 2013) and eating disorders (anorexia nervosa, AN and bulimia nervosa, BN) (Frank et al., 2000; Lawson et al., 2011, 2012), with highly heterogeneous and conflicting results (Al-Ayadhi, 2005; Alabdali et al., 2014; Emsley et al., 1989; Watson et al., 2007). The first aim of the present systematic review and preliminary meta-analysis was to test if the levels of these neuropeptides across different clinical samples and different biological fluids (plasma/serum, cerebrospinal fluid (CSF), urine and saliva) were consistently altered and could therefore be considered as potential reliable biomarkers for psychiatric disorders. The second aim was to investigate and address moderators and confounding factors impacting the preliminary meta-analytical estimates.

2. Methods

2.1. Selection procedures and data collection

2.1.1. Search strategies

A systematic search strategy was used to identify relevant articles. A two-step literature search was conducted by two independent researchers [GR, AS]. At a first step, the Web of Knowledge℠ database by Thomson Reuters® (including Web of Science™, BIOSIS Citation Index℠ and MEDLINE®) and Scopus® were searched. The search was extended until March 1st, 2015, including abstracts in English language only (see Supplementary materials for the electronic search code).

The second step involved the implementation of an electronic manual search of the reference lists of the retrieved articles. Articles identified through these two steps were then screened on basis of title or abstract reading. The articles surviving selection were fully downloaded (PDFs) and assessed for eligibility on the basis of full-text reading. Discrepancies were resolved through consensus with a third researcher [MR]. To achieve high quality of reporting we adopted MOOSE guidelines (Stroup et al., 2000) (see Supplementary materials).

2.1.2. Inclusion criteria

Articles meeting the inclusion criteria for the current systematic review and preliminary meta-analysis: (a) were original articles, written in English; (b) included subjects with a psychiatric diagnosis defined according to international standard definitions (ICD, DSM); c) included a healthy comparison group; d) reported sufficient data on peripheral (plasma, serum, urine, cerebrospinal fluid, saliva) OT or ADH level differences between groups (See Supplementary materials for details).

2.1.3. Exclusion criteria

We excluded (a) abstracts, pilot datasets, reviews, articles in language other than English; (b) articles failing to report enough data to perform a meta-analysis (we also contacted the authors to obtain the missing data); (c) articles with overlapping datasets. In case of multiple publications deriving from the same study population, we selected the articles reporting 1) the largest or 2) the most recent data set. In case of conflict between these two criteria, the sample size was prioritised.

2.1.4. Recorded variables

We recorded the following variables from each article: author, year of publication, quality of reporting criterion (adapted Newcastle-Ottawa Scale http://www.ohri.ca/programs/clinical_epidemiology/oxford. asp, see Supplementary material for detail), comparison group type (healthy comparisons), epidemiological data of patient and control samples (baseline sample sizes, mean age, proportion of females) and methodological information (specimen type, measurement method (ELISA, RIA), plasma extraction (yes/no)).

For the peripheral level of OT and ADH measured in plasma/serum, saliva, urine and CSF in patients and in controls, we extracted: mean value, standard deviation (SD), and standard error of the mean (SEM) (when presented instead of SD). We excluded data reporting OT or ADH peripheral levels following any drug administration.

2.2. Statistical analysis

2.2.1. Effect size

The meta-analyses were performed using Comprehensive Meta-Analysis Software version 2 (Borenstein et al., 2005). We did not perform analyses on diagnoses where there was only one study available. As a measure of effect size, Hedges' g was adopted. Results were Bonferroni-corrected for multiple testing, by dividing 0.05 by the overall number of meta-analyses conducted.

2.2.2. Heterogeneity, publication biases, sensitivity analysis

Heterogeneity among study point estimates was assessed using Q statistics (Paulson and Bazemore, 2010) and the proportion of the total variability in the effect size estimates evaluated with the I^2 index (Lipsey and Wilson, 2000). As meta-analysis of observational studies is supposed to be characterized by significant heterogeneity, random effect models were used (Cooper et al., 2009). Because of numerical constraints, meta-regressions were not conducted. Publication biases were tested with the Duval and Tweedie "trim and fill" method (Duval and Tweedie, 2000), when at least 3 studies were included. To further assess the robustness of the results, we performed sensitivity analyses by sequentially removing each study and re-running the analysis, when at least 5 studies were included (Higgins and Green, 2011). We conducted other sensitivity analyses to investigate the putative influence of several categorical moderators: assay technique, pregnancy, alcohol use and phase of the psychotic disorder. In particular, we performed sensitivity analyses to clarify the impact of peptide extraction techniques on the results. Because of numerical constraints, this was possible only in two of the subgroups (assessing plasma/serum ADH levels in MDD and psychosis). We performed an additional sub-group analysis dividing First Episode Psychosis (FEP) and chronic Psychosis vs healthy comparisons (see Supplementary materials for details). The potential influence of methodological weaknesses influencing preliminary meta-analytic estimates, according to the quality rating, was discussed.

3. Results

3.1. Database

After manual and electronic searches, 192 potential articles (PDFs) were screened to assess eligibility (see PRISMA flow chart eFig. 1 and MOOSE checklist eTable 1). 52 articles were considered eligible according to our inclusion criteria. 12 of these contributed two individual samples each: six investigating both OT and ADH in the same psychiatric disorder; four investigating the same neuropeptide across two different psychiatric disorders; two conducting the analyses on both plasma and CSF. Three articles delivered four individual samples each: two by measuring OT and ADH in two distinct diagnostic groups, and one measuring ADH both in plasma and CSF in two psychiatric disorders. Finally, one article delivered three individual samples, by addressing both neuropeptides in BN and only OT in AN. Consequently, the total number of eligible individual samples was 75. We did not perform analyses on diagnoses where there was only one study available: generalized social anxiety (GSAD) (Hoge et al., 2012), borderline personality disorder (BPD) (Bertsch et al., 2013), attention deficit and hyperactivity disorder (ADHD) (Taurines et al., 2014), Tourette syndrome (TS) (Leckman et al., 1994) and Prader-Willi syndrome (PWS) (Martin et al., 1998) (eTable 4). Therefore, the final database included 64 samples. Further details of the eligible articles not included in the meta-analysis and the list of the excluded articles (with reason for exclusion) are given in eTables 4 and 5. The full details of the included samples are appended in Table 1. The mean sample size of the included samples was of 63.64 ($\pm$36.50). Overall we performed 19 preliminary meta-analyses.

3.2. Preliminary meta-analyses of OT peripheral levels in psychiatric disorders

3.2.1. OT levels in CSF

Meta-analyses of OT levels in CSF were conducted in AN, BN, MDD, OCD and Psychosis. We found no differences between healthy comparisons and AN (n=2, overall sample=52, Hedges' g=−0.034, 95% CI from −1.068 to 1.019, p unc=0.950, between studies heterogeneity non-significant), BN (n=2, overall sample=86, Hedges' g=−0.219, 95% CI from −0.755 to 0.318, p unc=0.425, between studies heterogeneity non-significant), MDD (n=2, overall sample=75, Hedges' g=−0.333, 95% CI from −0.781 to 0.114, p unc=0.144, between studies heterogeneity non-significant), Psychosis (n=3, overall sample=147, Hedges' g=0.287, 95% CI from −0.330 to 0.903, p unc=0.362, substantial between studies heterogeneity Q=6.482, I^2=69.14, p=0.039), and OCD (n=2, overall sample=99, Hedges' g=0.599, 95% CI from 0.194 to 1.004, p unc=0.004, p corr=ns, between studies heterogeneity non-significant).

3.2.2. OT levels in plasma/serum

Meta-analyses of OT levels in plasma were conducted in ASD, BD, Psychosis and AN. They revealed no difference between healthy comparisons and patients diagnosed with ASD (n=4, overall sample=404, Hedges' g=−0.576, 95% CI from −1.442 to 0.291, p unc=0.193, considerable between studies heterogeneity Q=64.613, I^2=93.81, $p<0.001$), BD (n=3, overall sample=275, Hedges' g=0.056, 95% CI from −0.845 to 0.957, p unc=0.903, considerable between studies heterogeneity Q=20.796, I^2=90.38, $p<0.001$) or Psychosis (n=8, overall sample=691, Hedges' g=−0.005, 95% CI from −0.304 to 0.294, p unc=0.974, substantial between studies heterogeneity Q=24.923, I^2=71.91, p=0.001). Patients with AN had lower serum OT levels than healthy comparisons (n=2, overall sample=71, Hedges' g=−0.824, 95% CI from −1.308 to −0.341, p corr=0.001, between studies heterogeneity non-significant).

3.2.3. OT levels in saliva

Meta-analyses of OT levels in saliva were conducted in ADS. OT levels in saliva of ASD were not statistically different from those observed in healthy controls (n=2, overall sample=152, Hedges' g=−0.354, 95% CI from −0.701 to −0.006, p unc=0.046, p corr=ns, between studies heterogeneity non significant).

3.2.4. OT levels in urine

Meta-analyses were not performed as insufficient data were retrieved.

Table 1
Characteristics of studies included in the meta-analysis.

Study name	Year of publication	Country	Neuropeptide	Specimen	Diagnosis	Sample size			Age		Female %	
						Total	Pt[a]	HC[b]	Pt	HC	Pt	HC
Oxytocin in Autism Spectrum Disorders (7)												
Modahl et al. (1998)	1998	USA	OT[c]	Plasma	ASD[d]	59	29	30	8.1	8.8	0	0
(a) Al-Ayadhi (2005)	2005	Saudi Arabia	OT	Plasma	ASD	154	77	77	8.8		0.08	
(a) Miller et al. (2013)	2013	USA	OT	Plasma	ASD	75	40	35	12	12.29	0.48	0.46
Alabdali et al. (2014)	2014	Saudi Arabia	OT	Plasma	ASD	80	50	30	7	7.2	0	0
Feldman et al., (2014)	2014	Israel	OT	Saliva	ASD	79	39	40	5.28	4.46	0.14	0.14
Fujisawa et al. (2014)	2014	Japan	OT	Saliva	ASD	73	15	58	4.83	4.01	0.16	0.53
(a) Taurines et al. (2014)	2014	Germany	OT	Plasma	ASD	36	19	17	10.7	13.6	0	0
Oxytocin in Bipolar Disorder (3)												
Ozsoy et al. (2009)	2009	Turkey	OT	Serum	BD[e]	43	11	32		39.78		0.63
Turan et al. (2013)	2013	Turkey	OT	Serum	BD	91	67	24	34.63	34.42	0.46	0.41
(a) Rubin et al. (2014)	2014	USA	OT	Plasma	BD	141	75	66	34.7	37.18	0.55	0.58
Oxytocin in Major Depressive Disorder (2)												
(a) Pitts et al. (1995)	1995	USA	OT	CSF[f]	MDD[g]	37	19	18	37.3	30.7	0.47	0.5
(a) Sasayama et al. (2012)	2012	Japan	OT	CSF	MDD	38	17	21	39.5	38.3	0	0
Oxytocin in Psychosis (11)												
(a) Beckmann et al. (1985)	1985	Germany	OT	CSF	Psychosis	44	28	16	30.6	35	0	0.13
Glovinsky et al. (1994)	1994	USA	OT	CSF	Psychosis	55	40	15	29	30	0.23	0.33
Goldman et al. (2008)	2008	USA	OT	Plasma	Psychosis	22	15	7	40.88	34.7	0.6	0.43
Keri et al. (2009)	2009	Hungary	OT	Plasma	Psychosis	100	50	50	47.9	47.8	0.68	0.68
Rubin et al. (2010)	2010	USA	OT	Serum	Psychosis	108	50	58	30.94	27.73	0.46	0.54
(b) Sasayama et al. (2012)	2012	Japan	OT	CSF	Psychosis	48	27	21	42.6	38.3	0	0
(a) Rubin et al. (2013)	2013	USA	OT	Serum	Psychosis	76	38	38	23.71	27.89	0.37	0.37
Walss-Bass et al. (2013)	2013	USA	OT	Plasma	Psychosis	80	60	20	42.1	39.65	0.25	0.3
(a) Jobst et al. (2014)	2014	Germany and Austria	OT	Plasma	Psychosis	86	41	45	24.9	24.6	0	0
(b) Rubin et al. (2014)	2014	USA	OT	Plasma	Psychosis	157	91	66	34.7	37.18	0.55	0.58
(a) Strauss et al. (2015)	2015	USA	OT	Plasma	Psychosis	62	40	22	43.72	43.14	0.29	0.32
Oxytocin in Obsessive-Compulsive Disorder (2)												
(a) Leckman et al.(1994)	1994	USA	OT	CSF	OCD[h]	59	28	31	33.7	33	0.58	0.38
Altemus et al. (1999)	1999	USA	OT	CSF	OCD	40	14	26	35.4	35	0.5	0.46
Oxytocin in Anorexia Nervosa (4)												
(a) Demitrack et al. (1990)	1990	USA	OT	CSF	AN[i]	25	14	11	24.3	25.5	1	1
(a) Frank et al. (2000)	2000	USA	OT	CSF	AN	27	10	17	25.9	23.4	1	1
Lawson et al. (2011)	2011	USA	OT	Serum	AN	36	17	19	27.7	27.5	1	1
Lawson et al. (2012)	2012	USA	OT	Serum	AN	35	22	13	21.7	22	1	1
Oxytocin in Bulimia Nervosa (2)												
(b) Demitrack et al. (1990)	1990	USA	OT	CSF	BN[j]	46	35	11	24.4	25.5	1	1
(b) Frank et al. (2000)	2000	USA	OT	CSF	BN	40	23	17	26.4	23.4	1	1
Antidiuretic Hormone in Autism Spectrum Disorder (3)												
(b) Al-Ayadhi (2005)	2005	Saudi Arabia	ADH[k]	Plasma	ASD	154	77	77	8.8		0.08	
Boso et al. (2007)	2007	Italy	ADH	Plasma	ASD	39	18	21	27.5	29.6	0.11	0.14
(b) Miller et al. (2013)	2013	USA	ADH	Plasma	ASD	75	40	35	12	12.29	0.48	0.46
Antidiuretic Hormone in Bipolar Disorder (3)												
Padfield et al. (1977)	1977	UK	ADH	Plasma	BD	52	18	34			0.72	
(c) Rubin et al. (2014)	2014	USA	ADH	Plasma	BD	141	75	66	32.97	37.18	0.68	0.58
Antidiuretic Hormone in Major Depressive Disorder (6)												
(a) Sorensen et al. (1985)	1985	Denmark	ADH	CSF	MDD	98	46	52	46	46	0.74	0.58
(b) Sorensen et al. (1985)	1985	Denmark	ADH	Plasma	MDD	98	46	52	46	46	0.74	0.58
(b) Pitts et al. (1995)	1995	USA	ADH	CSF	MDD	37	19	18	37.3	30.7	0.47	0.50
Inder et al. (1997)	1997	New Zealand	ADH	Plasma	MDD	56	45	11	32.5	32.5	0.6	0.63
Heuser et al. (1998)	1998	Germany	ADH	CSF	MDD	62	37	25	46.8	65.5	0.7	0.32
van Londen et al. (1998)	1998	The Netherlands	ADH	Plasma	MDD	89	52	37	44.8	41.2	0.57	0.54
Rubin et al. (1999)	1999	USA	ADH	Plasma	MDD	40	20	20	40	38.44	0.6	0.6
Goldstein et al. (2000)	2000	USA	ADH	Plasma	MDD	42	21	21	40	40	0.48	0.48
Goekoop et al. (2006)	2006	The Netherlands	ADH	Plasma	MDD	98	81	17	40		0.67	
Antidiuretic Hormone in Psychosis (13)												
(b) Beckmann et al. (1985)	1985	Germany	ADH	CSF	Psychosis	44	28	16	30.6	35	0	0.13
(c) Sorensen et al. (1985)	1985	Denmark	ADH	CSF	Psychosis	61	9	52	29	46	0.33	0.58
(d) Sorensen et al. (1985)	1985	Denmark	ADH	Plasma	Psychosis	61	9	52	29	46	0.33	0.58
Emsley et al. (1989)	1989	South Africa	ADH	Plasma	Psychosis	51	23	28			0.30	0.25
Sarai and Matsunaga (1989)	1989	Japan	ADH	Plasma	Psychosis	60	37	23	44.6	34	0.3	0.52
Ohsawa et al. (1993)	1993	Japan	ADH	Plasma	Psychosis	30	15	15	32.2	27.3	0	0
Kudoh et al. (1998)	1998	Japan	ADH	Plasma	Psychosis	40	18	22	54	55.2	0.56	0.59
Elman et al. (2003)	2003	USA	ADH	Plasma	Psychosis	25	13	12	37.7	32.7	0.23	0.17
Ryan et al. (2004)	2004	UK	ADH	Plasma	Psychosis	24	12	12	34.8	35.8	0.42	0.42
Walsh et al., (2005)	2005	Ireland	ADH	Plasma	Psychosis	20	10	10	26.8	25	0	0
(b) Rubin et al. (2013)	2013	USA	ADH	Serum	Psychosis	76	38	38	23.71	27.89	0.37	0.37
(b) Jobst et al. (2014)	2014	Germany and Austria	ADH	Plasma	Psychosis	86	41	45	24.9	24.6	0	0
(d) Rubin et al. (2014)	2014	USA	ADH	Plasma	Psychosis	157	91	66	35.31	37.18	0.39	0.58
Antidiuretic Hormone in Obsessive-Compulsive Disorder (2)												
(a) Altemus et al. (1992b)	1992	USA	ADH	CSF	OCD	40	15	25	34.3	31.3	0.53	0.48
(b) Leckman et al. (1994)	1994	USA	ADH	CSF	OCD	59	28	31	33.7	33	0.58	0.38

Table 1 (*continued*)

Study name	Year of publication	Country	Neuropeptide	Specimen	Diagnosis	Sample size			Age		Female %	
						Total	Pt[a]	HC[b]	Pt	HC	Pt	HC
Antidiuretic Hormone in Anorexia Nervosa (4)												
(a) Gold et al. (1983)	1983	USA	ADH	CSF	AN	16	8	8	24.3	25.3	1	1
(b) Gold et al. (1983)	1983	USA	ADH	Plasma	AN	16	8	8	24.3	25.3	1	1
(c) Frank et al. (2000)	2000	USA	ADH	CSF	AN	50	33	17	26.2	23.4	1	1
Evrard et al. (2004)	2004	Belgium	ADH	Plasma	AN	24	12	12	21.6	22.8	1	1

[a] Pt, patients.
[b] HC, healthy controls.
[c] OT, oxytocin.
[d] ASD, autism spectrum disorder.
[e] BD, bipolar disorder.
[f] CSF, cerebrospinal fluid.
[g] MDD, major depressive disorder.
[h] OCD, obsessive-compulsive disorder.
[i] AN, anorexia nervosa.
[j] BN, bulimia nervosa.
[k] ADH, antidiuretic hormone.

Overall effect sizes are depicted in Fig. 1(a), forest plots are reported in supplementary materials (eFigs. 2 and 3) and eTable 6 report heterogeneity summary.

3.2.5. Publication biases and sensitivity analyses

The Duval and Tweedie's method showed that the results were not affected by publication biases. Sensitivity analysis removing one study per computation when at least 5 studies were included confirmed the robustness of the results (Higgins and Green, 2011).

3.3. Preliminary meta-analyses of ADH peripheral levels in psychiatric disorders

3.3.1. ADH levels in CSF

Meta-analyses of ADH levels in CSF were conducted in MDD, Psychosis, AN and OCD. There were no differences between healthy comparisons and patients diagnosed with MDD (n=3, overall sample=197, Hedges' g=−0.035, 95% CI from −.313 to 0.243, p unc=0.807, between studies heterogeneity non-significant), Psychosis (n=2, overall sample=105, Hedges' g=0.033, 95% CI from −0.424 to 0.491, p unc=0.886, between studies heterogeneity non-significant), AN (n=2, overall sample=66, Hedges' g=0.922, 95% CI from 0.243 to 1.602, p unc=0.008, p corr= ns, between studies heterogeneity non significant) and OCD (n=2, overall sample=99, Hedges' g=0.601, 95% CI from 0.198 to 1.003, p unc=0.003, p corr=ns, between studies heterogeneity non significant).

3.3.2. ADH levels in plasma/serum

Meta-analyses of ADH levels in plasma were conducted in ASD, BD, AN, MDD and Psychosis.

There were no differences between healthy comparisons and patients diagnosed with ASD (n=3, overall sample=268, Hedges' g=−0.086, 95% CI from −0.992 to 0.820, p unc=0.853, considerable between studies heterogeneity Q=23.590, I^2=91.52, $p<0.001$), BD (n=2, overall sample=193, Hedges' g=0.074, 95% CI from −0.850 to 0.998, p unc=0.875, considerable between studies heterogeneity Q=7.809, I^2=87.20, p=0.005), AN (n=2, overall sample=40, Hedges' g=−0.479, 95% CI from −1.508 to 0.551, p unc=0.362; between studies heterogeneity non-significant), MDD (n=6, overall sample=423, Hedges' g=−0.341, 95% CI from −0.078 to 0.759, p unc=0.111, substantial between studies heterogeneity Q=19.078, I^2=73.79, $p<0.001$), or Psychosis (n=11, overall sample=630, Hedges' g=−0.554, 95% CI from −0.966 to −0.142, p unc=0.008, p corr=ns, considerable between studies heterogeneity Q=55.984, I^2=82.14, $p<0.001$).

3.3.3. ADH levels in saliva and urine

Meta-analyses were not performed as insufficient data were retrieved.

Overall effect sizes are depicted in Fig. 1(b), forest plots are reported in Supplementary materials (eFigs. 4 and 5) and eTable 6 report heterogeneity summary.

3.3.4. Publication bias and sensitivity analyses

No significant publication bias emerged. In the MDD subgroup, sensitivity analysis revealed that overall plasma level of ADH were affected by inclusion of Sorensen et al. (1985). No significant difference emerged according to peptide extraction technique in MDD (total between group heterogeneity Q=0.021, df=1, p=0.884).

On the contrary, in the Psychosis subgroup, sensitivity analysis showed that the extraction technique could have an effect on the observed results (total between group heterogeneity Q=9.490, df=1, p=0.002), in that ADH levels resulted significantly impaired in Psychosis (n=6, overall sample=220, Hedges' g=−1.099, 95% CI from −1.617 to −0.581, p=0.001, considerable between studies heterogeneity Q=13.626, I^2=63.31, p=0.018) only in the group of studies employing peptide extraction (see Fig. 2).

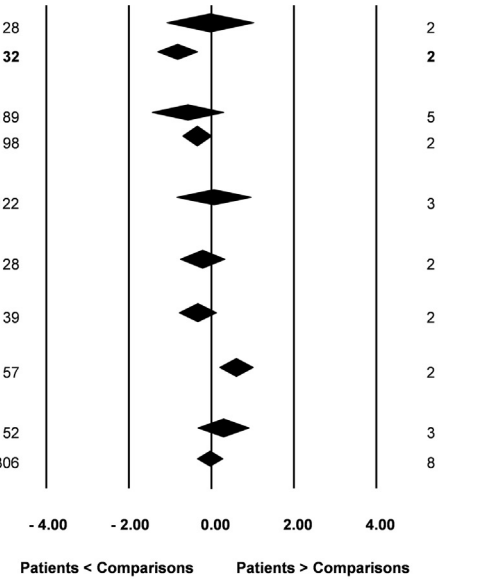
We also performed a sub-group analysis dividing First Episode Psychosis (FEP) and chronic Psychosis vs healthy comparisons. Three studies (Emsley et al., 1989; Rubin et al., 2013; Ryan et al., 2004) investigated peripheral levels of ADH in first-episode, drug naïve patients and eight (Beckmann et al., 1985; Elman et al., 2003; Jobst et al., 2014; Kudoh et al., 1998; Ohsawa et al., 1993; Rubin et al., 2014; Sarai and Matsunaga, 1989; Walsh et al., 2005) in chronic patients. There was no significant between-group heterogeneity (Q=6.228, df=1, p unc=0.013, p corr=ns).

3.4. Quality assessment

Table 2 describes the quality of the studies. Study quality scores ranged from 1 to 7 (median score was 4 out of 9 possible points). There were no significant differences in Newcastle-Ottawa Scale (NOS) scores between the subgroups (F=0.503, df=18, p=0.943). Unfortunately, since the number of studies included in each meta-analysis was too small to perform meta-regressions, it was not possible to directly assess the effect of NOS scores on the findings of our preliminary meta-analyses.

a) OT levels in psychiatric patients vs healthy comparisons

Diagnosis	Specimen	Statistics for each study					Sample size		n of studies included
		Hedges' g	Standard error	Lower limit	Upper limit	p-Value	Pt	Comp	
AN	CSF	-0.034	0.537	-1.086	1.019	0.950	24	28	2
AN	**serum**	**-0.824**	**0.247**	**-1.308**	**-0.341**	**0.001***	**39**	**32**	**2**
ASD	plasma	-0.576	0.442	-1.442	0.291	0.193	215	189	5
ASD	saliva	-0.354	0.177	-0.701	-0.006	0.046	56	98	2
BD	serum / plasma	0.056	0.460	-0.845	0.957	0.903	153	122	3
BN	CSF	-0.219	0.274	-0.755	0.318	0.425	37	28	2
MDD	CSF	-0.333	0.228	-0.781	0.114	0.144	36	39	2
OCD	CSF	0.599	0.207	0.194	1.004	0.004	42	57	2
Psychosis	CSF	0.287	0.315	-0.330	0.903	0.362	95	52	3
Psychosis	serum / plasma	-0.005	0.153	-0.304	0.294	0.974	385	306	8



b) ADH levels in psychiatric patients vs healthy comparisons

Diagnosis	Specimen	Statistics for each study					Sample size		n of studies included
		Hedges' g	Standard error	Lower limit	Upper limit	p-Value	Pt	Comp	
AN	CSF	0.922	0.347	0.243	1.602	0.008	41	25	2
AN	plasma	-0.479	0.525	-1.508	0.551	0.362	20	20	2
ASD	plasma	-0.086	0.462	-0.992	0.820	0.853	135	133	3
BD	plasma	0.074	0.471	-0.850	0.998	0.875	93	100	2
MDD	CSF	-0.035	0.142	-0.313	0.243	0.807	102	95	3
MDD	plasma	0.341	0.214	-0.078	0.759	0.111	265	158	6
OCD	CSF	0.601	0.205	0.198	1.003	0.003	43	56	2
Psychosis	CSF	0.033	0.233	-0.424	0.491	0.886	37	68	2
Psychosis	serum / plasma	-0.554	0.210	-0.966	-0.142	0.008	307	323	11

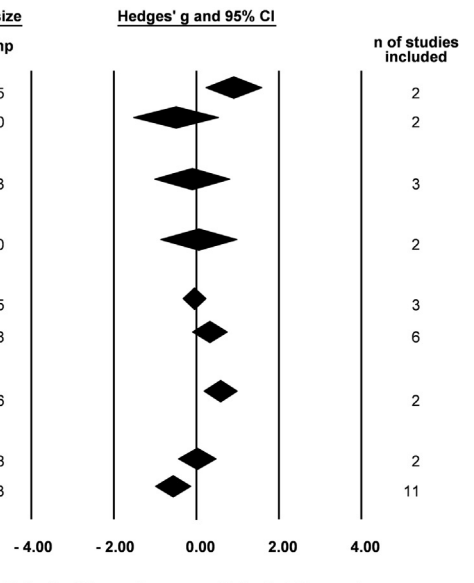


Fig. 1. Overall effect sizes for the comparison of OT and ADH levels in psychiatric patients vs healthy comparisons. Abbreviations: ADH, anti-diuretic hormone; AN, Anorexia Nervosa; ASD, Autism Spectrum Disorder; BD, Bipolar Disorder; BN, Bulimia Nervosa; CSF, Cerebral-Spinal Fluid; MDD, Major Depressive Disorder; OCD, Obsessive Compulsive Disorder; Pt, Patients. According to the Bonferroni correction, each hypothesis has been tested at a significance level of 0.002 (CI unadjusted). * $p < 0.002$.

4. Discussion

This is the first systematic review and preliminary meta-analysis to comprehensively summarize the available evidence of altered peripheral levels of OT and ADH in psychiatric disorders and investigate whether there are reliable differences which could serve as biomarkers between patients and healthy controls. We found no robust and convincing evidence for significant alterations in the two neuropeptides in psychiatric disorders.

The lack of significant association was secondary to high heterogeneity across individual studies, low quality and significant methodological limitations. Indeed, our results do not contradict the potential role of the two neuropeptides in mental disorders per se but do clearly suggest that peripheral levels do not reliably distinguish cases from controls. The putative reasons for this will be discussed in the following sections.

4.1. Reliability of assays

Both the commercially available immunoassays (RIA and EIA) have high heterogeneity and questionable validity (McCullough

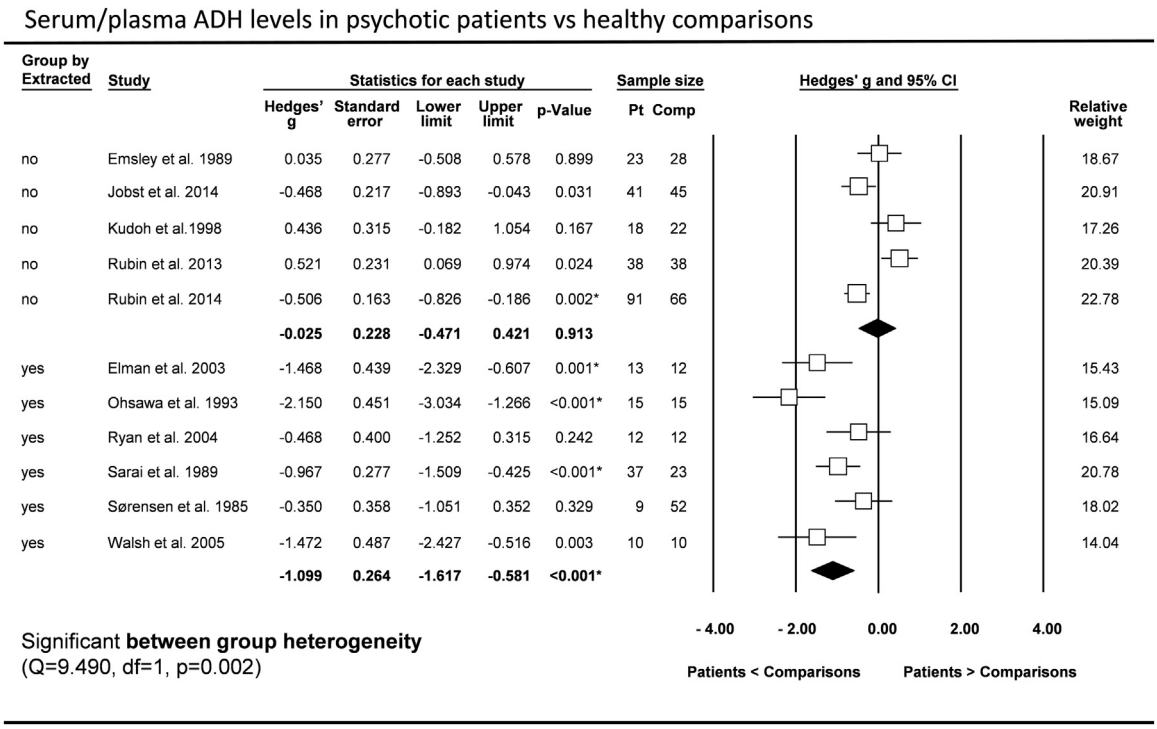


Fig. 2. Plasma/serum ADH levels in psychotic patients vs healthy comparisons according to peptide extraction technique. Abbreviations: ADH, anti-diuretic hormone; Pt, Patients. According to the Bonferroni correction, each hypothesis has been tested at a significance level of 0.002 (CI unadjusted).

et al., 2013). Average plasmatic levels within studies included in the present meta-analysis ranged from 0.64 pg/mL to 436.97 pg/mL for OT and from 0.66 pg/mL to 109.17 pg/mL for ADH, this variability being massively explained by the use of different immunoassay and by whether or not a pre-assay sample extraction was performed (eTable 2). It is evident, as others have previously suggested (Christensen et al., 2014), that the two immunoassays are poorly correlated, thus preventing the comparison of results obtained by different research groups. Particularly, in recent evaluations the RIA method was shown to have low sensitivity in the majority of samples tested (McCullough et al., 2013) and EIA performed without extraction yielded to values that were two orders of magnitude greater than those in extracted samples (Szeto et al., 2011) and without correlation, due to the presence of multiple adjunctive immunoreactive products besides oxytocin (Szeto et al., 2011). Since the main methodological concern specifically regards the use of extraction (Christensen et al., 2014), we performed a sensitivity analysis on the studies investigating serum/plasma ADH levels in Psychosis, which seemed to confirm that the extraction technique could have had an effect on the observed results. However, further characterization of the tagged molecules has shown that even in extracted samples the non-OT immunoreactive products of uncertain nature account for most of the measured immunoreactivity (McCullough et al., 2013). With respect to other bodily fluids, such as saliva and urine, it has been demonstrated that the estimated levels are highly discrepant and weakly correlated to plasmatic levels (McCullough et al., 2013).

4.2. Recommendations for methodological improvement

It is of crucial importance that future research in this field aim at method validation and standardization before the results of studies exploring the role of neuropeptides in physiology and disease can be considered meaningful.

The samples obtained by EIA, even following the assay manufacturers' recommendations to extract samples, contain multiple non-OT immunoreactive molecules, still to identify. It is therefore pivotal to clarify whether those are reflecting the turnover of bioactive OT, or are non-related reactants. Moreover, assays with high degree of sensitivity and specificity, such as two-dimensional liquid chromatography separation with tandem mass spectrometry detection, could be used as reference for validation of techniques as RIA and EIA and to confirm the presence of OT and ADH in other biological fluids, such as saliva and urine, where less knowledge is available.

Furthermore, pre-analytical errors should be avoided and systematic evaluation and standardization of pre-analytical procedures should be conducted. In particular, consideration should be payed to variations in the levels of the hormones related to circadian patterns and other physiological conditions (e. g., fasting or post-prandial state, sexual activity, menstrual cycle, pregnancy), time of day and environmental features during collection, tube additives (e. g., EDTA and citrate), use of protease inhibitors and storage conditions.

4.3. Peripheral vs central levels

Our results provide meta-analytical confirmation for the concern, increasingly expressed by many authors, about the lack of neurophysiological evidence of a direct relationship between peripheral levels of OT and ADH and their central release and activity (Grinevich et al., 2015; Kagerbauer et al., 2013; Leng and Ludwig, 2015; Ludwig and Leng, 2006; McCullough et al., 2013; Neumann, 2007). Originally, ADH and OT have been described as hormones, involved respectively in antidiuresis, osmolality regulation, direct vasoconstriction and hepatic glycogenolysis (Appelgren, 1982; Robertson, 2001) and labor (Husslein, 1984), lactation (Crowley, 2015), and sexual activity (Carmichael et al., 1987). Under physiological conditions, the primary drive for ADH peripheral secretion is plasma osmolality. It is unlikely that this homeostatic constraint can be chronically overridden by erratic triggers, such as socioemotional stimuli (Kagerbauer et al., 2013).

Table 2
Modified Newcastle-Ottawa Quality Assessment Scale for case-control studies included in the meta-analysis.

Study name and Year of publication	Total	Selection[a]				Comparability[b]	Exposure[c]		
		Diagnostic adequacy	Representativeness of the cases	Selection of controls	Definition of controls		Ascertainment of OT/ ADH level	Same method of ascertainment for cases and controls	Missing data rate
Plasma/Serum Oxytocin in Autism Spectrum Disorders									
Modahl et al., 1998)	6	⋆	/	⋆	⋆	⋆	/	⋆	⋆
(a) Al-Ayadhi (2005)	3	⋆	/	/	/	⋆	/	⋆	/
(a) Miller et al. (2013)	4	⋆	/	/	/	⋆	/	⋆	⋆
Alabdali et al. (2014)	3	⋆	/	/	/	⋆	/	⋆	/
(a) Taurines et al. (2014)	6	⋆	/	/	⋆	⋆⋆	/	⋆	⋆
Overall	4.60 (± 1.817)								
Saliva Oxytocin in Autism Spectrum Disorders									
Feldman et al. (2014)	5	⋆	/	/	⋆	⋆⋆	/	⋆	/
Fujisawa et al. (2014)	4	⋆	/	⋆	/	⋆	/	⋆	/
Overall	4.50 (± 0.707)								
Plasma/Serum Oxytocin in Bipolar Disorder									
Ozsoy et al. (2009)	1	⋆	/	/	/	/	/	/	/
Turan et al. (2013)	4	⋆	/	/	⋆	/	/	⋆	⋆
(a) Rubin et al. (2014)	7	⋆	/	/	⋆	⋆⋆	⋆	⋆	⋆
Overall	4.00 (± 3.00)								
CSF Oxytocin in Major Depressive Disorder									
(a) Pitts et al. (1995)	4	⋆	/	/	⋆	/	/	⋆	⋆
(a) Sasayama et al. (2012)	5	⋆	/	/	⋆	⋆⋆	/	⋆	/
Overall	4.50 (± 0.707)								
CSF Oxytocin in Psychosis									
(a) Beckmann et al. (1985)	3	⋆	⋆	/	/	/	/	⋆	/
Glovinsky et al. (1994)	1	⋆	/	/	/	/	/	/	/
(b) Sasayama et al. (2012)	5	⋆	/	/	⋆	⋆⋆	/	⋆	/
Overall	3.00 (± 2.00)								
Plasma/Serum Oxytocin in Psychosis									
Goldman et al. (2008)	1	/	/	/	/	/	/	⋆	/
Keri et al. (2009)	4	⋆	/	/	/	⋆⋆	/	⋆	/
Rubin et al. (2010)	3	⋆	/	/	⋆	/	/	⋆	/
(a) Rubin et al. (2013)	6	⋆	⋆	⋆	⋆	⋆	/	⋆	/
Walss-Bass et al. (2013)	7	⋆	⋆	⋆	⋆	⋆	/	⋆	⋆
(a) Jobst et al. (2014)	4	⋆	/	/	/	⋆⋆	/	⋆	/
(a) Rubin et al. (2014)	7	⋆	/	/	⋆	⋆⋆	⋆	⋆	⋆
(a) Strauss et al. (2015)	5	⋆	/	/	⋆	⋆⋆	/	⋆	/
Overall	4.63 (± 2.066)								
CSF Oxytocin in Obsessive-Compulsive Disorder									
(a) Leckman et al. (1994)	5	⋆	/	/	/	⋆⋆	⋆	⋆	/
Altemus et al. (1999)	3	⋆	/	/	/	⋆	/	⋆	/
Overall	4.00 (± 1.414)								
CSF Oxytocin in Anorexia Nervosa									
(a) Demitrack et al. (1990)	2	⋆	/	/	/	/	/	⋆	/
(a) Frank et al. (2000)	6	⋆	/	⋆	⋆	⋆⋆	/	⋆	/
Overall	4.00 (± 2.828)								
Plasma/Serum Oxytocin in Anorexia Nervosa									
Lawson et al. (2011)	7	⋆	⋆	⋆	⋆	⋆⋆	/	⋆	/
Lawson et al. (2012)	7	⋆	⋆	⋆	⋆	⋆⋆	/	⋆	/
Overall	7.00 (± 0.000)								
CSF Oxytocin in Bulimia Nervosa									
(b) Demitrack et al. (1990)	2	⋆	/	/	/	/	/	⋆	/
(b) Frank et al. (2000)	6	⋆	/	⋆	⋆	⋆⋆	/	⋆	/
Overall	4.00 (± 2.828)								

Plasma/Serum Antidiuretic Hormone in Autism Spectrum Disorder									
(b) Al-Ayadhi (2005)	3	⋆	/	/	/	⋆	/	⋆	/
Boso et al. (2007)	7	⋆	/	⋆	⋆	⋆	⋆	⋆	⋆
(b) Miller et al. (2013)	4	⋆	/	/	/	⋆	/	⋆	⋆
Overall	4.67 (± 2.082)								
Plasma/Serum Antidiuretic Hormone in Bipolar Disorder									
Padfield et al. (1977)	1	/	/	/	/	/	/	⋆	/
(c) Rubin et al. (2014)	7	⋆	/	/	⋆	⋆⋆	⋆	⋆	⋆
Overall	4.00 (± 4.243)								
CSF Antidiuretic Hormone in Major Depressive Disorder									
(a) (Sorensen et al. (1985)	2	⋆	/	/	/	/	/	⋆	/
(b) Pitts et al. (1995)	4	⋆	/	/	⋆	/	/	⋆	⋆
Heuser et al. (1998)	4	⋆	/	/	⋆	/	⋆	⋆	/
Overall	3.33 (± 1.155)								
Plasma/Serum Antidiuretic Hormone in Major Depressive Disorder									
(b) Sorensen et al. (1985)	2	⋆	/	/	/	/	/	⋆	/
Inder et al. (1997)	4	⋆	/	/	⋆	/	/	⋆	⋆
van Londen et al. (1998)	4	⋆	/	/	⋆	/	/	⋆	⋆
Rubin et al. (1999)	5	⋆	/	/	⋆	⋆⋆	/	⋆	/
Goldstein et al. (2000)	4	⋆	/	/	/	⋆	/	⋆	⋆
Goekoop et al. (2006)	3	⋆	/	/	/	/	/	⋆	⋆
Overall	3.67 (± 1.033)								
CSF Antidiuretic Hormone in Psychosis									
(b) Beckmann et al. (1985)	3	⋆	⋆	/	/	/	/	⋆	/
(c) Sorensen et al. (1985)	2	⋆	/	/	/	/	/	⋆	/
Overall	2.50 (± 0.707)								
Plasma/Serum Antidiuretic Hormone in Psychosis									
(d) Sorensen et al. (1985)	2	⋆	/	/	/	/	/	⋆	/
Emsley et al. (1989)	2	/	/	/	/	/	/	⋆	⋆
Sarai and Matsunaga (1989)	2	⋆	/	/	/	/	/	⋆	/
Ohsawa et al. (1993)	3	⋆	/	/	/	⋆	/	⋆	/
Kudoh et al. (1998)	3	/	/	/	/	⋆⋆	/	⋆	/
Elman et al. (2003)	5	⋆	/	⋆	⋆	/	/	⋆	⋆
Ryan et al. (2004)	6	⋆	/	/	⋆	⋆⋆	⋆	⋆	/
Walsh et al. (2005)	5	⋆	/	/	⋆	⋆	⋆	⋆	/
(b) Rubin et al. (2013)	6	⋆	⋆	⋆	⋆	⋆	/	⋆	/
(b) Jobst et al. (2014)	4	⋆	/	/	/	⋆⋆	/	⋆	/
(d) Rubin et al. (2014)	7	⋆	/	/	⋆	⋆⋆	⋆	⋆	⋆
Overall	4.09 (± 1.814)								
CSF Antidiuretic Hormone in Obsessive-Compulsive Disorder									
Altemus et al. (1992a)	3	⋆	/	/	⋆	/	/	⋆	/
(b) Leckman et al. (1994)	5	⋆	/	/	/	⋆⋆	⋆	⋆	/
Overall	4.00 (± 1.414)								
CSF Antidiuretic Hormone in Anorexia Nervosa									
(a) Gold et al. (1983)	2	/	/	/	/	⋆	/	⋆	/
(c) Frank et al. (2000)	6	⋆	/	⋆	⋆	⋆⋆	/	⋆	/
Overall	4.00 (± 2.828)								
Plasma/Serum Antidiuretic Hormone in Bulimia Nervosa									
(b) Gold et al. (1983)	2	/	/	/	/	⋆	/	⋆	/
Evrard et al. (2004)	5	⋆	⋆	/	/	⋆⋆	/	⋆	/
Overall	3.50 (± 2.121)								

[a] Selection: (1) Diagnostic adequacy: A, yes, with independent validation ⋆; B, yes, e.g. record linkage or based on self reports; C, no description. (2) Representativeness of the cases: A, consecutive or obviously representative series of cases ⋆; B, potential for selection biases or not stated. (3) Selection of controls: A, community controls (same community as cases) ⋆; B, hospital controls; C, no description. (4) Definition of controls: A, no history of Diagnosis ⋆; B, no description of source.

[b] Comparability: Comparability of cases and controls on the basis of the design or analysis: A, study controls for sex and age ⋆; B, study controls for any additional factor ⋆.

[c] Exposure: (1) Ascertainment of OT/ADH level: A, laboratory analyst where blind to case/control status ⋆; B, laboratory analyst not blinded to case/control status; C, no description. (2) Same method of ascertainment for cases and controls: A, yes ⋆; B, no. (3) Missing data rate: A, same rate for both groups ⋆; B, non respondents described; C, rate different and no designation.

On the other hand plasma OT levels are stable, except in pregnancy (Leng and Ludwig, 2015), but may be regulated independently from central OT as suggested by converging evidence from animal studies (Ludwig et al., 1994; Moos et al., 1989). In humans no correlation was found between central and plasma OT in pregnant women (Altemus et al., 2004) and suicide attempters (Jokinen et al., 2012).

The mechanisms explaining such dissociation between central and peripheral compartments are barely understood. Separate and independent neuropeptide synthesis and vesicle routing and targeting have been shown in the somata (for peripheral secretion and somatic release) and in dendrites (for dendritic release), which might account for independent central and peripheral release patterns (Landgraf and Neumann, 2004). The axons of the magnocellular neurons (MCN) of the PVN and SON nuclei of the hypothalamus project to the posterior pituitary from which they can be secreted into the peripheral bloodstream to exert their hormonal actions (Ludwig and Leng, 2006; Marazziti and Catena Dell'osso, 2008). A substantial amount of ADH and OT are released from soma and dendrites into the extracellular space, where the neuropeptides act as autocrine or paracrine signals and diffuse toward distant brain sites. The axons of the parvocellular neurons of the PVN project centrally (Ludwig and Leng, 2006). Axonal and dendritic/soma release may be independently regulated by the MCNs through inhibitory mechanisms – mediated by corticosterone, GABA, endogenous opioids, the atrial natriuretic peptide and ADH itself – which selectively block the peripheral secretion (Wotjak et al., 1998).

The utility of CSF assays is more controversial. In fact, although the extracellular fluid of the brain interconnects freely with the CSF, the contribution of centrally released neuropeptides to CSF levels depends on several factors, as they eventually reach the CSF after having induced central effects by binding to specific receptors and having been possibly degraded by enzymes. It is plausible that once diffused in the CSF, the neuropeptides may have lost their biological activity, since they are unlikely to pass back into the brain parenchyma against the concentration gradient to act on their receptors. Furthermore, the blood-brain barrier prevents ADH and OT to reflow into the central compartment (i. e. brain parenchyma and CSF) once they have reached the peripheral one (i. e., blood and peripheral organs) (Kagerbauer et al., 2013; Mens et al., 1983). Further, peptides appear to have a short plasma half-life (1–2 min) and a slightly longer central half-life (~30 min) (MacDonald and MacDonald, 2010). Given to a positive feedback, once dendritic release is triggered, it is self-sustaining and long-lasting (Ludwig and Leng, 2006). Priming persisting for at least 90 min (Ludwig et al., 2002) allows peptides to survive for long enough to diffuse to distant sites. Also long-lasting changes induced in other transmitter systems may further extend their biological activity and behavioural effects (MacDonald and MacDonald, 2010; Uvanas-Moberg et al., 2005).

4.4. Psychosis

Overall, we found no convincing evidence that either plasmatic or CSF ADH and OT levels are altered in Psychosis. We also investigated whether the peripheral ADH impairments in Psychosis were associated with the illness phase. It has been argued that psychotic exacerbations may be concurrent with a transient reset of the osmostasis for ADH secretion, elevated plasma levels of the neuropeptide and eventually water imbalance, as an epiphenomenon of dysfunctions in hypothalamic pituitary adrenal (HPA) axis response to psychological stimuli (Goldman, 2009). However, we found no meta-analytical evidence for peripheral ADH differences between first episode and chronic Psychosis.

Despite this findings should be interpreted in the light of a body of literature that has demonstrated a role for these neuropeptides in functions which map on to common symptoms and behavioural deficits in psychosis and schizophrenia, in particular in the social cognition domain (MacDonald and MacDonald, 2010). There is considerable evidence of a role these two neuropeptides in various aspects of social behaviour. For example, OT alters response to social cues (Zak et al., 2005) and has an effect on emotion recognition/theory of mind (Domes et al., 2007; Guastella et al., 2010b), fearful face processing (Evans et al., 2010), social anxiety (Heinrichs et al., 2003), paranoia (Legros et al., 1992), and trust behaviour (Baumgartner et al., 2008). Research with ADH in human social cognition is less prevalent but there is evidence that intranasal ADH biases emotional face perception (Thompson et al., 2004)), enhances memory encoding of human faces (Guastella et al., 2010b), produces gender-specific changes in perceived friendliness of others, and alters autonomic response to threatening faces (Thompson et al., 2006). ADH has been shown to alter reciprocation of cooperation in males (Rilling et al., 2014) while the ADH Avpr-1a gene, which is involved in social bonding in humans (Walum et al., 2008), has been shown to influence the money people will give to others in an economic game (Knafo et al., 2008). As the present analysis investigates between-group differences, not within-group effects our results do not contradict the potential role of these neuropeptides in the symptoms of psychosis per se. In schizophrenia, patients have been shown to produce a failure in the trust-related increases in OT seen in controls (Keri et al., 2009) and OT levels have been shown to correlate inversely with symptomatology (including suspiciousness and paranoia) and prosociality (Rubin et al., 2010), as well as capacity to identify facial emotions (Goldman et al., 2008). Neuroleptics have also been reported to normalise raised ADH plasma levels in patients with schizophrenia (Raskind et al., 1987).

Furthermore, there is also emerging preclinical and clinical evidence supporting the potential for manipulation by exogenous delivery of these two neuropeptides. Administration of OT either intracerebrally or subcutaneously effectively reverted behavioural deficits in rodent models of schizophrenia (Macdonald and Feifel, 2012). Single-dose studies in humans proved OT ability to improve the processing of emotional and social stimuli in subjects affected by schizophrenia (MacDonald and MacDonald, 2010). Finally, the results of two recent clinical trials of exogenous OT (intranasal administration; dose: 24 IU twice daily (Pedersen et al., 2011) and 40 IU twice daily (Feifel et al., 2010)) in patients with schizophrenia suggest a therapeutic effect across different symptom domains with good safety and tolerability both in short-term and long-lasting use. Nevertheless, a recent meta-analysis examining the effects of OT on psychotic symptoms and social cognition found weak and inconsistent evidence, mainly because of methodological limitations, similarly as the ones observed by our current analysis (Gumley et al., 2014).

4.5. ASD

We did not find evidence that peripheral ADH and OT levels are impaired in ASD, in contrast with converging evidence from animal models of ASD and human studies which implicate alterations in the function of the OT system within ASD. The results align with concerns that these measures are not reliable proxies of the central release and activity of these neuropeptides. In preclinical animal models of neurodevelopmental disorders, autistic-like symptoms were shown to be accounted by alterations of trafficking and/or release of OT from axonal terminals and to be rescued after OT administration (Grinevich et al., 2015). Clinical trials with exogenous OT, administered either via intravenous infusion or intranasal spray, have produced contradictory results, ranging from positive outcomes in a variety of ASD psychopathology

domains, namely emotion recognition (Guastella et al., 2010a), social cognition (Andari et al., 2010), and core autistic repetitive behaviours (e.g. ordering, compulsion to tell/ask and touching) (Hollander et al., 2003), to modest (Anagnostou et al., 2012) or null clinical improvement (Anagnostou et al., 2014). Although ADH is less commercially available, the few reports to date show some promise that ADH may exert gender-specific positive effects on processes related to empathic ability (Thompson et al., 2006). Nevertheless the findings in human studies should be interpreted cautiously and confirmed in larger trials.

4.6. BD and MDD

Plasmatic and CSF neuropeptide levels were not significantly altered in affective disorders (BD and MDD) compared to matched healthy controls.

Again these results indicate that peripheral OT and ADH levels are not reliable biomarkers of BD/MDD. In contrast to the null findings shown here, several preclinical and clinical data provide evidence of the association between ADH and affective disorders (BD and MDD). ADH is involved in the regulation of the hypothalamus-pituitary-adrenal (HPA) axis, which has been found to be overactive in BD (Cervantes et al., 2001; Daban et al., 2005) and MDD (Carroll et al., 1981; Dinan, 1994; Holsboer, 2000). Post-mortem brain tissues of patients with MDD and BD contain a greater number of ADH-immunoreactive neurons in the hypothalamic PVN (Merali et al., 2006). Therefore, antagonists of V1b receptor have been developed and tested in rodents as potential new strategies for the treatment of affective disorders, whose efficacy in humans does still need clarification (Griebel et al., 2012).

4.7. OCD, AN and BN

Our meta-analysis did not detect significant alterations of ADH and OT in OCD and BN. A difference in serum OT levels could be observed between patients suffering from AN and healthy comparisons. The reliability of peripheral ADH and OT levels as biomarkers of AN is weakened by the global hypothalamic-pituitary dysfunction, the impact of fluid and sodium restriction and purging behaviours observed in AN and the putative role of the two hormones in the regulation of the gut brain axis and energy homeostasis (Blevins and Ho, 2013). In fact, both neuropeptide levels end to be restored after body weight recovery (Gold et al., 1983). Therefore, once again our findings should be interpreted considering that peripheral levels of OT and ADH are unreliable proxy measures of their central activity.

4.8. Limitations

There are some significant limitations to our study. The subgroups were very small in sample sizes. However, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions meta-analyses provide statistical combination of results from two or more separate studies ((Higgins and Green, 2011), Chapter 9, page 244). The studies included were highly heterogeneous. For example, despite evidence that patients with schizoaffective psychoses may have clear distinctive features as compared to schizophrenic psychoses (Pagel et al., 2013), they were included in some of the articles in the Psychosis subgroup (OT: 6 out of 11 (Goldman et al., 2008; Rubin et al., 2014, 2013, 2010; Strauss et al., 2015; Walss-Bass et al., 2013)); ADH (4 out of 13 (Emsley et al., 1989; Ohsawa et al., 1993; Rubin et al., 2014, 2013)). Correspondingly, psychotic features were unevenly considered as exclusion criteria across the articles investigating affective disorders (BD and MDD). Several confounding factors might have had an impact on the results. 38% of the included studies reported that participants were taking lithium salts (eTable 3). Despite its therapeutic value, lithium exerts adverse effects on the kidney, leading to nephrogenic diabetes insipidus (NDI) in up to 10% of the patients on long term treatment (Bendz and Aurell, 1999; Bendz et al., 1996), which may be expected to be associated with a compensatory increase in ADH release (Watson et al., 2007). As regard OT, preclinical studies in rats found that a systemic injection of lithium leads to a significant elevation of peripheral OT levels (Cui et al., 2001; You et al., 2001). Furthermore, 42 studies out of 62 (68%) failed to control for alcohol intake (not applicable to 2 studies which had recruited only children), which was reported to induce degeneration in numerous neurons in the hypothalamic magnocellular system in rats (Silva et al., 2002). The majority of studies did not ascertain the pregnancy state of female participants (70%, 35 out of 50, condition not applicable to 14 studies because of the characteristics of the sample, see eTable 3 for further details). During pregnancy dramatic structural and functional changes occur in the OT system of the mother's brain (Hillerer et al., 2014; Rocchetti et al., 2014). Moreover, high levels of oxytocinase secreted by the placenta might further contribute to the final serum/plasma OT levels (Nomura et al., 2005). Finally, only 18% of the studies investigating OT and none of those investigating ADH analyzed the fluctuations of OT levels across the menstrual cycle phases. Studies investigating plasma OT and ADH levels during the menstrual cycle in different species, including humans, found that these fluctuate across the ovarian cycle (Wathes and Swann, 1982). (Spruce et al., 1985). As a consequence, our meta-analytical estimates are affected by high uncertainty and should be considered as a preliminary synthesis of the available literature.

5. Conclusions

The current meta-analysis does not provide convincing evidence that peripheral OT or ADH levels are altered in psychiatric disorders as compared to healthy controls. These findings are characterized by high heterogeneity, various methodological limitations, and poor quality. For more meaningful results to be obtained, methods need to be validated and standardized. Future studies are requested to better address with robust methods and adequate sample sizes the actual role of ADH and OT as biomarkers of mental illnesses.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2016.04.117.

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